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Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial

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Author Contributions

HW designed and implemented the study with ECOG-ACRIN with substantial input from JS and SR. HW, SK, WT, DG, SG, AA, NL, SA, JR, JP, MS, SM, RP, AT, CB, TE, AS, AC, SK, LH, SR, and JS recruited patients and collected data. HW and SD analyzed and interpreted the data with substantial input from SR and JS. HW, SD, and JS wrote the report with input from all listed co-authors. All authors reviewed the report and gave final approval to submit for publication.

Declaration of interests

HW reports honoraria from Peregrine, honoraria from ACEA, grants and honoraria from Pfizer, honoraria from Helsinn, grants and honoraria from Genentech/Roche, grants from Clovis, grants from Exelixis, grants from AstraZeneca/Medimmune, grants from BMS, grants from Gilead, grants from Novartis, grants from Xcovery, grants from Celgene, grants from Pharmacyclics, grants from Lilly, outside the submitted work. SD reports research grants from NIH-NCTN to ECOG-ACRIN and grants from Genentech during the conduct of the study; personal fees from AstraZeneca, outside the submitted work. In addition, SD has a patent, Methods of Assessing Tumor Growth, for Dana-Farber Cancer Institute, Patent Application No. PCT/US2014/054821, pending. SK, following completion of the study and presentation at the World Lung Conference, left the clinical practice of Thoracic Surgery at the Montefiore Medical Center and joined Merck on November 28, 2016 as a Senior Principal Scientist in the Lung Oncology Group. SM reports personal fees from Clovis, grants and personal fees from Pfizer, grants from Amgen, personal fees and research funding from Bristol-Myers Squibb, research funding from Merck, research funding from Bayer, research funding from Janssen, grants from Celgene, outside the submitted work. RP received honoraria from Roche/Genentech for advisory boards and educational speaking engagements. TE reports personal frees from Genentech, outside the submitted work. LH reports personal fees from AbbVie advisory board, pro bono from Bristol Myers Squib advisory board, pro bono from Boehringer Ingelheim advisory board, personal fees from Lilly advisory board, personal fees from Genentech-Roche advisory board, payment to institution from Merck advisory board, pro bono from Xcovery consulting, pro bono from Bayer consulting, outside the submitted work. SR reports advisory board from Amgen, AstraZeneca, AbbVie, Boehringer Ingelheim, BMS, Lilly, Celgene, Genentech, and Novartis, outside the submitted work. JS reports research grants from National Cancer Institute during the conduct of the study; grants from Genentech, personal fees from Genentech, grants from Lilly, personal fees from Lilly, outside the submitted work. The other authors declared no conflicts of interest.

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SUMMARY

Background—Adjuvant chemotherapy for resected early stage NSCLC provides modest survival benefit. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, improves outcomes when added to platinum-based chemotherapy in advanced stage non-squamous NSCLC. We conducted a phase III study to evaluate the addition of bevacizumab to adjuvant chemotherapy in early stage resected NSCLC (E1505). The primary endpoint was overall survival.

Methods—Adult patients (≥ 18 years old) with ECOG performance status 0 or 1 with completely resected stage IB (≥4 centimeters) to IIIA (AJCC 6th edition) NSCLC were enrolled within 6–12 weeks of surgery and stratified by chemotherapy regimen, stage, histology, and sex. Minimum mediastinal lymph node sampling at specified levels was required (level 7 and 4 for right-sided tumors or level 7 and 5 and/or 6 for left-sided tumors). Normal laboratory values within two weeks of randomisation were required for enrollment. Chemotherapy, which was selected for each patient prior to randomisation, consisted of four, 3-week (21-day) cycles of cisplatin (75 mg/m^2 in all regimens) with either vinorelbine 30 mg/m^2 days 1 and 8; docetaxel 75 mg/m^2 day 1; OR gemcitabine 1200 mg/m^2 days 1 and 8; OR, starting in 2009 with an amendment, pemetrexed 500 mg/m^2 day 1 along with B12 and folic acid supplementation. Patients were randomised 1:1 to Arm A (chemotherapy) or Arm B, adding bevacizumab at 15 mg/kg every 3 weeks starting with cycle 1 of chemotherapy and continuing for one year. Randomisation to treatment arm was performed centrally and determined using permuted blocks within strata with dynamic balancing on institution. The study had 85% power to detect a 21% reduction in the overall survival (OS) hazard rate with a one-sided 0·025-level test. The primary endpoint was overall survival, which was defined as the time from randomisation to death from any cause, and patients who were thought to be alive at the time of final analysis were censored at the last date of contact with analysis done based on intention to treat. This is final analysis of the primary endpoint of overall survival of E1505 (NCT00324805).

Findings—From July 2007 to September 2013, 1501 patients were enrolled, of whom 26% (N=383) had stage IB, 44% (N=636) stage II, and 30% (N=439) stage IIIA) with 28% (N=422) squamous cell histology. Cisplatin-based chemotherapy regimens utilized were vinorelbine 25% (N=377), docetaxel 23% (N=343), gemcitabine 19% (N=283), and pemetrexed 33% (N=497). At a median follow-up time of 50·3 months (IQR 32.9–68.0), estimated OS hazard ratio (B/A) was 0·99 (95% CI: 0·82–1·19, p=0·90). The median OS on Arm A has not been reached and is 85.8 months (95% CI 74.9-NA) on Arm B. Statistically significantly increased grade 3–5 toxicities of note (all attributions) included: overall worst grade (ie all grade 3/4/5 toxicities) (67%(N=496) versus 83% (N=610)); hypertension (8%(N=60) versus 30%(N=219)), and neutropenia (33%(N=241) versus 37%(N=275)) on Arms A and B, respectively. There was no significant difference in grade 5 adverse events per arm (N=15 on arm A and N=19 on arm B).

Interpretation—The addition of bevacizumab to adjuvant chemotherapy failed to improve overall survival for patients with surgically resected early stage NSCLC. Bevacizumab does not have a role in this setting and should not be considered as an adjuvant therapy for resected NSCLC patients.

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INTRODUCTION

Complete surgical resection remains the most effective initial therapy for patients with early stage non-small cell lung cancer (NSCLC). Adjuvant chemotherapy became a standard after the 2003 presentation of the International Adjuvant Lung Cancer Trial (IALT) (n=1,867)[1] with a reported 4% absolute five-year survival benefit and an overall survival hazard ratio (OS HR) =0·86 (95% CI: 0·76–0·98, P<0·03) in favor of adjuvant cisplatin-based chemotherapy for 4 cycles. Two other positive adjuvant chemotherapy trials, which utilized only cisplatin with vinorelbine, maintained significantly improved survival benefits with long-term follow-up.[2,3] More specifically, the ANITA trial, which included a mix of stage IB, II and IIIA patients, reported a median overall survival of 65·7 months (95% CI 47·9–88·5) in the chemotherapy arm compared to 43·7 months (95% CI 35·7–52·3) with observation.[4] Meta-analyses of NSCLC adjuvant chemotherapy trials confirmed the 4–5% absolute survival increase at 5 years.[5,6] Thus, current guidelines endorse the use of adjuvant cisplatin-based chemotherapy for stage II and IIIA NSCLC after complete resection.[7,8] Adjuvant cisplatin-based chemotherapy doublets for stage I patients is often suggested for patients with larger stage I (N0) tumors at ≥ 4 centimeters based on improved survival in subset analyses from the earlier adjuvant trials.[3,9]

In the setting of advanced stage NSCLC, the first agent to improve survival when added to a platinum doublet was bevacizumab. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), improved response, progression-free survival, and overall survival when added to carboplatin/paclitaxel in advanced stage non-squamous NSCLC in the E4599 trial.[10] Based on those positive results, this phase III trial (E1505) was designed to assess whether the addition of bevacizumab to cisplatin-based chemotherapy would improve survival of patients with resected early stage NSCLC in the adjuvant setting, who despite adjuvant chemotherapy remain at high risk of relapse.

In the LACE meta-analysis of adjuvant chemotherapy trials, cisplatin/vinorelbine was associated with a superior survival benefit compared to the other regimens.[11] In addition to cisplatin/vinorelbine we decided to include other standard cisplatin-based doublet regimens utilized for stage IV NSCLC in E1505, including cisplatin/gemcitabine and cisplatin/docetaxel given their efficacy in the metastatic setting and practice patterns. In 2009 cisplatin/pemetrexed was also included in E1505 for non-squamous patients following FDA approval of that regimen in advanced NSCLC. Subsequently a phase II trial that demonstrated that cisplatin/pemetrexed was better tolerated than cisplatin/vinorelbine in the adjuvant setting.[12] Patients with squamous histology were included in E1505, based on the assumption that the hemoptysis seen more frequently with bevacizumab in metastatic squamous lung cancer patients would be unlikely in patients post-resection. However, patients with squamous histology were not permitted to receive adjuvant pemetrexed/cisplatin based on inferior outcomes with this regimen in advanced stage squamous lung carcinoma patients.

METHODS

Study design and participants

This open-label predominantly North American Intergroup phase III trial was led by the ECOG-ACRIN Cancer Research Group coordinating center and approved by the ethics committee of every participating center and undertaken according to the Declaration of Helsinki. All patients gave written informed consent prior to participation. Eligible patients had undergone complete resection of stage IB (≥ 4 centimeters), II or IIIA NSCLC no less than 6 weeks and no more than 12 weeks prior to enrollment and had recovered from surgery. Staging was completed per AJCC 6th edition. Mediastinal lymph node sampling at specified levels was required (level 7 and 4 for right-sided tumors or level 7 and 5 and/or 6 for left-sided tumors). Patients were at least 18 years old with ECOG performance status 0 or 1. No prior systemic chemotherapy was allowed but patients with a prior cured malignancy treated with surgery, biologic, or hormonal cancer therapy or radiation therapy was allowed if all treatment was completed at least 5 years prior to randomisation. Normal laboratory values within two weeks of randomisation were required including platelet and neutrophil counts within normal limits (WNL), normal coagulation studies, liver function within 5 times the upper limit of normal (ULN), adequate renal function (creatinine no more than 1·5 times ULN), and urine protein creatinine spot test WNL or validated with a 24-hour urine collection. Patients assigned to pemetrexed/cisplatin were also required to have a calculated creatinine clearance ≥ 45mL/min using the standard Cockcroft and Gault formula. Patients were excluded for active arterial thrombotic disease (including myocardial infarction) within 12 months prior to randomisation. Patients with any history of cerebral vascular accident (CVA) or transient ischemic attack (TIA) were excluded. All women of childbearing potential had a negative pregnancy test within 2 weeks prior to randomisation and both fertile men and women must have agreed to use adequate contraceptive measures during study treatment. Patients must not have had any clinically significant ongoing, active, or serious infection; symptomatic or uncontrolled congestive heart failure; symptomatic or uncontrolled cardiac arrhythmia; or any other medical condition or psychiatric illness/social situations that would limit compliance with study requirements.

Patients were excluded for history of bleeding diathesis or coagulopathy; uncontrolled hypertension; use of dipyridamole, ticlopine, clopidogrel, and/or cilostazol; serious non-healing wound, ulcer, bone fracture, or having undergone a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomisation OR core biopsy within 7 days prior to randomisation. Patients were excluded for any abdominal abscess or perforation within 28 days of randomisation or anticipated surgery during course of the study, or ongoing post-operative hemoptysis.

Randomisation and masking

Randomisation was performed using permuted blocks within strata with dynamic balancing on main ECOG-ACRIN institutions plus affiliates. The randomisation was stratified based on the patients planned chemotherapy (cisplatin/vinorelbine, cisplatin/docetaxel, cisplatin/gemcitabine, cisplatin/pemetrexed); stage of disease (IB (>=4cm), II, IIIA-N2, IIIA-T3N1); histology (squamous cell, other NSCLC) and gender (male or female). No masking was performed and all patients and care team members were aware of treatment assignments. The only masking that occurred was during Data Safety and Monitoring Committee (DSMC) meetings during which the DSMC was blinded to treatment arm during assessments of efficacy and toxicity at the pre-defined analysis time points.

Procedures

All patients were to receive up to 4 cycles of 21 days of cisplatin given at 75 mg/m^2 on day 1, in combination with a third generation cytotoxic agent. The other chemotherapy agents based on investigator's choice were: vinorelbine 30 mg/m^2 days 1 and 8; docetaxel 75 mg/m^2 day 1; gemcitabine 1200 mg/m^2 days 1 and 8; and starting in 2009 with an amendment, pemetrexed 500 mg/m^2 day 1 along with B12 (1000 micrograms intramuscularly at least every 9 weeks while on therapy starting at a minimum on the first day of therapy and folic acid supplementation (at 400 micrograms daily orally). The investigator was required to indicate the selected chemotherapy regimen for the patient prior to randomisation. Patients randomised to Arm B also received bevacizumab administered with chemotherapy for a total of 4 cycles and continued every 21 days for up to 1 year (measured from first day of protocol treatment). Bevacizumab was dosed at 15 mg/kg IV on day 1 of each cycle.

Dose interruptions and dose reductions for the chemotherapy drugs followed standard practice guidelines. If a dose delay was required for 1 drug, both chemotherapy drugs (and bevacizumab for arm B) were delayed and resumed together so that they remained in sync. Day 1 chemotherapy could only be administered for absolute neutrophil count of at least 1,500/mm2 and platelet count of at least 100,000/Ul. Treatment could be delayed for up to 3 weeks to allow for recovery of counts. If febrile neutropenia was documented cisplatin doses were not adjusted, but vinorelbine, docetaxel, gemcitabine or pemetrexed were reduced by 1 dose level for first event and by 2 dose levels for the 2nd episode and protocol chemotherapy was discontinued for a third episode. Dose level 1 was 25% of original dosing and dose level 2 was 50% of original dosing. Cisplatin dose reductions by 25% were permitted for grade 3 nausea/vomiting despite maximum supportive care or grade 3 oral mucositis. Cisplatin was reduced by 50% for creatinine of >1.5–2.0 times the upper limit of normal (ULN) and held

if > 2.0 times the ULN, but could be restarted with 25% reduction if the creatinine improved within 3 weeks. Both chemotherapeutic agents were held for sensory/motor neuropathy or grade 2 or higher and resumed after recovery to grade 1 (with 25% reduction if max grade was 2 and 50% reduction if maximum grade was 3 or higher). Cisplatin was discontinued for grade 3 or 4 hearing loss. For hepatic toxicity: vinorelbine or docetaxel or pemetrexed was reduced by 25% for grade 2 hepatic toxicity and held for grade 3 or higher with resumption only if recovery within 3 weeks. For any clinically significant grade 3 or 4 toxicity felt to be related to chemotherapy the treatment was delayed until recovery to at least grade 1, then resumed with a 25% dose reduction in the agent felt most likely to have caused the toxicity. Further dose reductions were permitted per investigator discretion and discontinuation of protocol chemotherapy was required if such toxicity did not resolve to at least grade 1 within 3 weeks. For patients on arm B, continuation of bevacizumab was permitted despite early discontinuation of chemotherapy.

Particular for docetaxel, if an allergic reaction/anaphylaxis event occurred, the drug was stopped and diphehydramine and dexamethasone were given with a resumption of a slower infusion. If the symptoms recurred then docetaxel was discontinued. In such instances, after discussion with study chair, the patient was permitted to switch to another chemotherapy arm, or if on arm B could continue on bevacizumab alone. For Day 8; vinorelbine or gemcitabine were reduced to 75% dose for ANC of 500–999 × 10^6/L or platelet count of 50,000–74,999 × 10^6/L or held for lower results of either ANC or platelets.

Patients continued protocol therapy up to 4 cycles of chemotherapy and, for those on arm B, up to 1 year of bevacizumab (counted from first day of therapy) unless there was evidence of recurrent NSCLC, development of second primary cancer (excluding non-melanoma skin cancer or carcinoma in situ of the cervix), or in the situation that continuation on protocol was felt to be detrimental to the patient’s health due to extraordinary medical circumstances.

Bevacizumab was never dose reduced, but was to be delayed if chemotherapy was delayed to allow for same day administration. If chemotherapy was withheld (skipped) bevacizumab was given on schedule. Bevacizumab was discontinued for hemoptysis of > grade 1, grade 3 or 4 congestive heart failure, evidence of reversible posterior leukoencephalopathy syndrome, grade 4 allergic reaction, grade 2 or higher arterial thrombosis, grade 4 hypertension, nephrotic syndrome, hemorrhage of grade 2 or higher in the central nervous system or > grade 2 elsewhere, wound dehiscence requiring intervention, perforation of gastrointestinal track, or any other grade 3 or 4 clinically significant adverse event attributable to bevacizumab that did not resolve in 4 weeks of holding drug (grade 3) or had not resolved to grade 1 and with approval of study chair (grade 4).

Post-operative radiation therapy was not permitted. Patients were seen at least every 3 weeks with a full physical examination including blood pressure and laboratory studies (including a complete blood count and comprehensive metabolic panel) and assessment for adverse events during the period of chemotherapy administration.

Patients on Arm B were required to have visits with physical examination, adverse event assessments and laboratory studies every 6 weeks while receiving single agent bevacizumab.

All patients were followed for recurrence with chest imaging (radiograph or computed tomography which were reviewed locally) and physical examination every 3 months for 2 years, then every 6 months through year 5, then annually through year 10.

Outcomes

The primary objective of this phase III study was to compare the overall survival in patients with NSCLC randomised to chemotherapy with bevacizumab (Arm B) and without bevacizumab (Arm A) in an intent-to-treat analysis. Overall survival was defined as the time from randomisation to death from any cause, and patients who were thought to be alive at the time of final analysis were censored at the last date of contact. Secondary objectives included disease-free survival as well as toxicity assessment defined as toxicity with chemotherapy with or without bevacizumab used in the adjuvant setting in patients with resected NSCLC. Other secondary objectives, included to perform analyses of tissue and blood to establish factors that predict for clinical outcome in patient receiving chemotherapy, with or without bevacizumab, for resected early stage NSCLC. To determine whether smoking status is linked to outcome for patients with resected early stage NSCLC treatment with chemotherapy with or without bevacizumab in the adjuvant setting.

Statistical analysis

All analyses were conducted on an intent to treat basis. All randomised patients were included in the primary analyses and DFS analysis. For toxicity data, only patients who received therapy were included. All patients were otherwise assessable. The randomisation was stratified based on planned chemotherapy backbone (cisplatin/vinorelbine, cisplatin/docetaxel, cisplatin/gemcitabine, cisplatin/pemetrexed); stage of disease (IB (≥4 cm), II, IIIA-N2, IIIA-T3N1); histology (squamous cell, non-squamous NSCLC); and sex (male or female), using permuted blocks within strata with dynamic balancing on main ECOG institutions plus affiliates. The statistical design targeted an overall survival (OS) hazard ratio (HR) or 0.79 with 85% power while maintaining a significance level of 2·5% in a one-sided test. Assuming exponential event times, the corresponded to an improvement in the median OS of 66 months on Arm A to 83.5 months on Arm B. The total planned accrual goal was 1500 patients with full statistical information at 676 deaths.

The study design specified interim analyses starting at 25% information (167 events) and every 6 months thereafter with stopping rules defined for efficacy with a truncated O'Brien-Fleming boundary and for futility with repeated confidence intervals. The study was continuously monitored for toxicity signals, particularly the rates of grade 3–5 arterial thromboembolic events and bleeding events, as well as the rate of grade 4–5 wound healing complications.

OS was defined as the time from randomisation to death from any cause, and patients who were thought to be alive at the time of final analysis were censored at the last date of contact. Disease-free survival (DFS) was defined as the time from randomisation to an event defined as disease recurrence, new primary of lung cancer, second primary, or death, whichever occurred first. Patients who did not experience a DFS event at analysis were censored at

their last date of disease assessment. Time to treatment discontinuation was measured in months from date of registration to date off treatment.

Event-time distributions were estimated using the Kaplan-Meier method. Cox proportional hazards models stratified on the randomisation stratification factors were used to estimate the hazard ratios and to test for differences between treatment arms. Adverse events, reported using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4·0, were compared using the Fisher's exact test; cumulative incidence of treatment discontinuation was estimated using a competing risks model.[13] All reported P values are two-sided, and CIs are at the 95% level. R version 2.10.0 was used for statistical analyses. This study is registered with ClinicalTrials.gov, NCT00324805.

Role of the funding source

Funding for this trial was provided by the National Cancer Institute of the National Institutes of Health of the United States and was coordinated by the ECOG-ACRIN Cancer Research Group Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs). The funds were provided to ECOG-ACRIN to support protocol development and conduct including auditing and data analysis. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between study activation on June 1, 2007 and enrollment termination on September 20, 2013, a total of 1501 patients were enrolled across the United States National Clinical Trials Network (NCTN) and the Cancer Clinical Trials Group (formerly NCIC-CTG). All 1501 patients are included in the OS and DFS analyses, which were done on an intent to treat basis. Twenty-nine patients never started assigned therapy (12 on Arm A and 17 on Arm B) as noted in the study Consort Diagram (Figure 1 due to treatment refusal (N=14), ineligibility (N=4), progression before start of therapy (N=4), other medical issue (N=7)). A total of 234 patients (15·6%, 121 on Arm A and 113 on Arm B) were deemed ineligible most commonly for inadequate nodal sampling (N=101) or ineligible stage (N=44). Other reasons for ineligibility were registration < 6 weeks from surgery (N=45), elevated baseline blood pressure or inadequate documentation of baseline blood pressure (N=15), baseline UPC not obtained in time frame (N=20), history of malignancy (N=2), inadequate renal function (N=2) and a variety of individual reasons including incorrect pathology, history of infarction, active claudication, missing baseline performance status, history of prior chemotherapy. The majority of these were identified as ineligible on retrospective central review after initiating (and most commonly after completing) therapy. As was standard on ECOG-ACRIN trials during the time of enrollment on E1505, neither centralized screening nor pre-screening strategies were utilized. The median follow-up on patients still alive was 50·3 months (IQR 32.9–68.0)(51·7 mos (IQR 34.7–68.9) on Arm A and 48·1 (IQR31.1–67.0) mos on Arm B).

Patient demographics and disease characteristics were well balanced by treatment Arm and are summarized in Table 1. Of the full 1501 randomized patients (749 on arm A with chemotherapy alone and 752 on arm B with the addition of bevacizumab), a majority of the patients were white and 50% (N=746) were male. Squamous cell histology was reported for 28% (N=422) of patients (29% (N= 216) Arm A and 27% (N=206) Arm B). The largest proportion of patients (44%, N=636) had stage II disease with 26% (N=383) stage IB and 30% (N=439) stage IIIA. The vast majority of patients were treated with a lobectomy (77% (N=577/749) Arm A, 74% (N=557) Arm B) and 11% (N=81) on Arm A had a pneumonectomy compared to 14% (N=103) on Arm B. Systematic lymph node sampling was reported for 46% (N=689) of patients on trial and a complete mediastinal lymph node dissection was reported for 46% (N=346) Arm A and 47% (N=355) of Arm B. When compared to data used as stratification factors, on-study reporting of chemotherapy choice was discordant in 0·7% (10/1500 cases with data); pathologic subtype was discordant in 3·7% (55/1500 cases with data); sex was discordant in 0·5% (8/1501 cases with data); and stage was discordant in 14·1% (206/1458 cases with data).

All chemotherapy options were utilized with 25% (N=377) of patients receiving cisplatin/vinorelbine, 23% (N=343) cisplatin/docetaxel, 19% (N=283) cisplatin/gemcitabine, and 33% (N=497) cisplatin/pemetrexed. The median number of treatment cycles was 4 on Arm A (range: 1–4; IQR: 4-4) and 9 on Arm B (range: 1–18; IQR: 4–17) (IQR = Interquartile Range). The majority of patients on Arm A (81·3%, N=599/737) completed therapy per protocol (4 cycles or approximately 3 months), however only 36·6% (N=269/735) of patients on Arm B completed all planned therapy (a total of 12 months of therapy). The number of patients who discontinued therapy for adverse events on arm A was 62/737 (8.4%) compared to 203/735 (27.6%) on arm B. The remaining patients came off trial for early progression (N= 7 and 35 on arms A and B respectively), patient decision to withdraw (N=51/737 (6.9%) and 174/735 (23.7%) on arms A and B respectively), and other issues such as alternative therapy, and other complicating disease (N= 27/737 (3.7%) and 54/735 (7.3%) on arms A and B respectively). In interpreting these results it is critical to bear in mind that arm A patients were only on therapy for up to 3 months, compared with up to 12 months with bevacizumab on arm B. All patients who received any therapy were included in the toxicity analyses (N=1473, 738 on Arm A and 735 on Arm B). The reporting of grade 1 events was not required per protocol. Reporting of grade 2 events that were unexpected and related was required, but given uncertainty about expected toxicity with bevacizumab in the adjuvant setting, and the fact that only arm B patients were considered to be receiving an investigational agent, toxicity reporting was skewed towards arm B. A table of grade 1 and 2 events that were reported in at least 10% of patients is included (Table 2), but all listed events (anemia, fatigue, creatinine increased and decreased neutrophil count) are expected events with platinum based chemotherapy. All post-baseline grade 3–5 adverse events of any attribution that occurred in at least 1% of patients are included in Table 3. Full details of post-baseline grade 3–5 adverse events of any attributions are available in the Supplemental materials (pages 6–10). Adverse events associated with anti-angiogenic therapy such as hypertension were more common for patients treated with bevacizumab. Statistically significantly increased grade 3–5 toxicities of note (all attributions) included: overall worst grade (ie all grade 3/4/5 toxicities) (67%(N=496) versus 83%(N=610)); hypertension (8%

(N=60) versus 30%(N=219)), and neutropenia (33%(N=241) versus 37%(N=275)) on Arms A and B, respectively. There was no significant difference in deaths while on treatment per arm (N=15 on arm A and N=19 on arm B) (supplemental material page 11). Of the 15 deaths on arm A, only 3 (thromboembolic event, stroke and sepsis) were considered at least possibly related to therapy. Of the 19 deaths on arm B, 10 were considered at least possibly related (multiorgan failure, febrile neutropenia, sudden death, myocardial infraction, bronchopulmonary hemorrhage, aspiration, bronchopleural fistula, wound dehiscence, lung infection (N=2)). Other causes of death that were not considered related were on arm A: atrial fibrillation, death (or sudden death) NOS (N=6), thromboembolic death, adult respiratory distress syndrome, other neoplasm, respiratory failure, other cardiac disorder. For arm A the non-related causes of death were: death NOS (N=5), myocardial infraction, hypoxia, sepsis, other neoplasm.

After the 6th planned interim analysis, the independent data safety and monitoring committee recommended release of the study results since the repeated confidence interval (A/B) (0·77 – 1·33) barely included the alternative of interest, and because the estimated conditional power of the trial was estimated to be 4·1% (standard error = 0·006). At previous interim analyses, early stopping criteria for efficacy and futility were not met. The results reported here include data after 475 survival events (241 on Arm A and 234 on Arm B); this represents 70% (475/676) of the planned full information for the final analysis and is considered the final analysis. The estimated median OS on Arm A has not been reached; for Arm B it was 85·8 mos (74·9 - NA). The estimated OS hazard ratio (B/A) was 0·99 (95% CI: 0·82–1·19, p=0·90). Figure 2A illustrates OS by treatment arm for the primary analysis (ITT) population while Figure 2B is OS in a sensitivity analysis among eligible patients (n=1267) demonstrating similar results. A forest plot of OS hazard ratios for various subgroups is displayed in Figure 3.

A total of 724 patients have experienced a recurrence or death (DFS event) (360 on Arm A and 364 on Arm B). The estimated median DFS and corresponding 95% CI on each treatment arm was 42·9 mos (36·7–57·0 mos) on Arm A and 40·6 mos (35·5–49·5 mos) on Arm B. Figure 4A displays DFS by treatment arm for the primary analysis (ITT) population. A sensitivity analysis among eligible patients (n=1267) was conducted with similar results and are displayed in Figure 4B. The estimated DFS hazard ratio (B/A) was 0·99 (95% CI: 0·86–1·15, p=0·95). For DFS, the forest plot of hazard rations for various subgroups is displayed in Figure 5. A total of 607 recurrences were reported and 56·5% (342/605) of them were biopsied. Sites of recurrence were reported as follows: lung (n=299, 37%), liver (n=40, 5%), central nervous system (n=122, 15%), subcutaneous and lymph node (n=126, 16%), skeletal (n=113, 14%), other sites (n=110, 14%), and unknown site (n=1). More than one site could have been reported at the time of a recurrence.

The DFS and OS results across all stratification factors including stage, sex, and histology appear consistent with the overall outcomes of the study. The subset analysis by chemotherapy is immature at this time with the median follow-up by chemotherapy choice at 54·3 months (IQR 34.7–71.5) on vinorelbine, 60·3 months (IQR 41.2–76.0) on docetaxel, 57·0 months (IQR 36.4–71.4) on gemcitabine, and only 40·6 months (IQR 29.3–52.9) on pemetrexed.

DISCUSSION

The addition of bevacizumab to four cycles of adjuvant cisplatin based chemotherapy for resected early stage NSCLC failed to improve OS, the primary endpoint of this trial. The estimated OS hazard ratio (B/A) was 0·99 (95% CI: 0·82–1·19, p=0·90). Thus, four cycles of cisplatin based adjuvant chemotherapy remains the standard of care for patients with resected stage II and IIIA NSCLC and is also considered for many patients with resected stage IB NSCLC with larger tumors (at least 4 centimeters in size). Though bevacizumab has improved response rate, PFS, and survival in advanced non-squamous NSCLC when combined with carboplatin/paclitaxel[10] an OS benefit was not seen when bevacizumab was combined with other platinum doublets for advanced stage NSCLC, most notably with cisplatin/gemcitabine in the AVAiL trial.[14] The results of E1505 demonstrate that the addition of bevacizumab to adjuvant chemotherapy failed to improved outcomes in patients with resected NSCLC, as it has also failed with adjuvant regimens for colon cancer[15–17], breast cancer[18], and melanoma.[19]

The median overall survival of E1505 was 85·6 months for patients on Arm B and in excess of 85 months for Arm A, although this could change with longer follow-up (median follow-up not mature). However, these survival results appear to surpass the median OS of 65·7 months reported in the ANITA adjuvant trial, which served as our control arm estimate for this trial. The survival difference is nearly 20 months despite the fact that bevacizumab was not additive, and thus patients received no other therapeutic intervention beyond that given on ANITA. The DFS in our trial was 40·6 months on Arm B and 42·9 months on Arm A versus 36·3 months DFS on the ANITA trial, a difference of 7 months at most. Thus, the relative OS benefit seen on E1505 is far in excess of the DFS change seen over time between the two trials. Likely this in part reflects careful selection of patients with better imaging modalities available to detect more advanced stage disease prior to resection, and also the availability of more modalities to treat patients who have recurred or perhaps the use of modern chemotherapy regimens in this study. Completion of four cycles of adjuvant chemotherapy was higher on E1505 than ANITA, which may also have contributed. Though any comments on why completion of chemotherapy was higher on E1505 than ANITA is highly speculative, it may be related to better tolerability of the newer chemotherapeutic options and also to improved supportive medications. ANITA did also have a slightly higher proportion of stage IIIA patients (>35% compared to ~30% on E1505) but that was offset by a high percentage of stage I patients as well (36% on ANITA versus 25% on E1505).

The potential reasons behind the lack of survival benefit in early stage disease with bevacizumab could be attributed to the relatively modest therapeutic effects of this agent in advanced stage disease, lack of predictive biomarkers for patient selection, and activation of alternative biological pathways to promote angiogenesis. Biomarker analyses from tumor samples of patients enrolled to E1505 are planned to understand the biology underlying disease recurrence, and to determine whether a sensitive subset to bevacizumab could be identified.

Limitations of this trial include the prolonged enrollment period, the high percentage of ineligible patients, and emerging data over the course of the trial that bevacizumab in

subsequent trials in advanced stage NSCLC and in the adjuvant setting with other malignancies did not perform at the level envisioned based on the E4599 results. The lack of a biomarker for bevacizumab was another significant limitation that prevented us from identifying a patient population who may have benefitted from adjuvant bevacizumab.

E1505 was not designed to compare chemotherapy regimens and at this point no clear differences have emerged yet. However, follow-up is limited particularly with the cisplatin/pemetrexed group as that regimen was added later in the trial. Longer follow-up and additional detailed analyses of these data accounting for potential imbalances in prognostic factors between treatment arms within the subgroups are needed before any conclusions of an effect of chemotherapy choice on outcomes can be made. The ongoing JIPANG trial (UMIN000006737) in Japan is randomizing 800 patients with resected NSCLC to cisplatin/pemetrexed versus cisplatin/vinorelbine and will provide prospective data to answer the question of whether or not there are meaningful differences in outcomes with these two chemotherapy doublets. We also did not find any meaningful differences in subgroup analyses, but hope that as the molecular analyses and other correlative work with the tissue and blood samples collected on the trial is completed that it may shed some light on relevant biologic markers that can help in the better defining which patients are most likely to benefit from adjuvant chemotherapy.

Areas of ongoing research for adjuvant treatment of advanced stage NSCLC include targeted tyrosine kinase inhibitor use in patients with resected NSCLC harboring an activating mutation in the epidermal growth factor receptor (EGFR) or translocation in anaplastic lymphoma kinase (ALK), but this is a small subset of patients. The PD-1 checkpoint inhibitors nivolumab and pembrolizumab and the PD-L1 inhibitor atezolizumab are approved for the second-line treatment of advanced stage NSCLC, with recent positive data in first-line metastatic disease for a subset of patients. Phase III trials are ongoing with each of these agents, as well as similar check point inhibitors, as adjuvant therapy for resected early stage NSCLC. E1505 provides definitive evidence that bevacizumab should not be used in the adjuvant setting for resected early stage NSCLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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PANEL: RESEARCH IN CONTEXT

Evidence before this study

In developing the study design and protocol, we did a systematic review of the scientific literature. We searched PubMed, with no time restrictions; abstracts of major oncology meetings; and trial websites, including ClinicalTrials.gov, for preclinical data and clinical trials (phase I, II, III) published in English that assessed patients with non-small-cell lung cancer (NSCLC) who were treated with adjuvant chemotherapy, and also searched for studies with bevacizumab in the context of metastatic NSCLC, and in the adjuvant setting for any malignancy. We used the search terms: lung cancer, NSCLC, adjuvant chemotherapy, peri-operative chemotherapy, neo-adjuvant chemotherapy, adjuvant therapy, post-operative chemotherapy, neo-adjuvant chemotherapy, adjuvant therapy, bevacizumab. Clinical data in support of this trial included phase 3 trials demonstrating a survival benefit in NSCLC patients who were treated with adjuvant chemotherapy after surgical resection and phase 3 trials demonstrating a response rate and progression free survival benefit with the addition of bevacizumab to platinum doublet chemotherapy in patients with metastatic NSCLC. An overall survival benefit with the addition of bevacizumab was demonstrated in the E4599 trial, in which the agent was added to first-line carboplatin and paclitaxel chemotherapy in patients with metastatic NSCLC. Based on the survival benefit seen with adjuvant platinum doublet chemotherapy after surgical resection in early stage NSCLC and the survival benefit seen with the addition of bevacizumab to platinum doublet chemotherapy in metastatic disease, we postulated that the addition of bevacizumab to platinum doublet adjuvant chemotherapy in early stage NSCLC would result in a survival benefit.

Added value of this study

Our study demonstrated that despite the additive benefit of bevacizumab to platinum doublet chemotherapy in patients with metastatic lung cancer, no differences in disease free survival or overall survival were seen on the bevacizumab arm of this trial in patients with resected early stage NSCLC. We did not identify any subsets of patients with benefit or any with unexpected harm with the combination.

Implications of all the available evidence

Based on the results of this trial the use of bevacizumab as a post-operative adjuvant regimen in patients with NSCLC is not advised. During the period of time of the study conduct and analysis adjuvant trials of bevacizumab in other malignancies were reported and were similarly negative for any benefit in overall survival. The overall outcomes of this trial did demonstrate an improvement in overall survival compared to historical controls, reflecting other improvements in lung cancer outcomes for patients with resected early stage NSCLC.

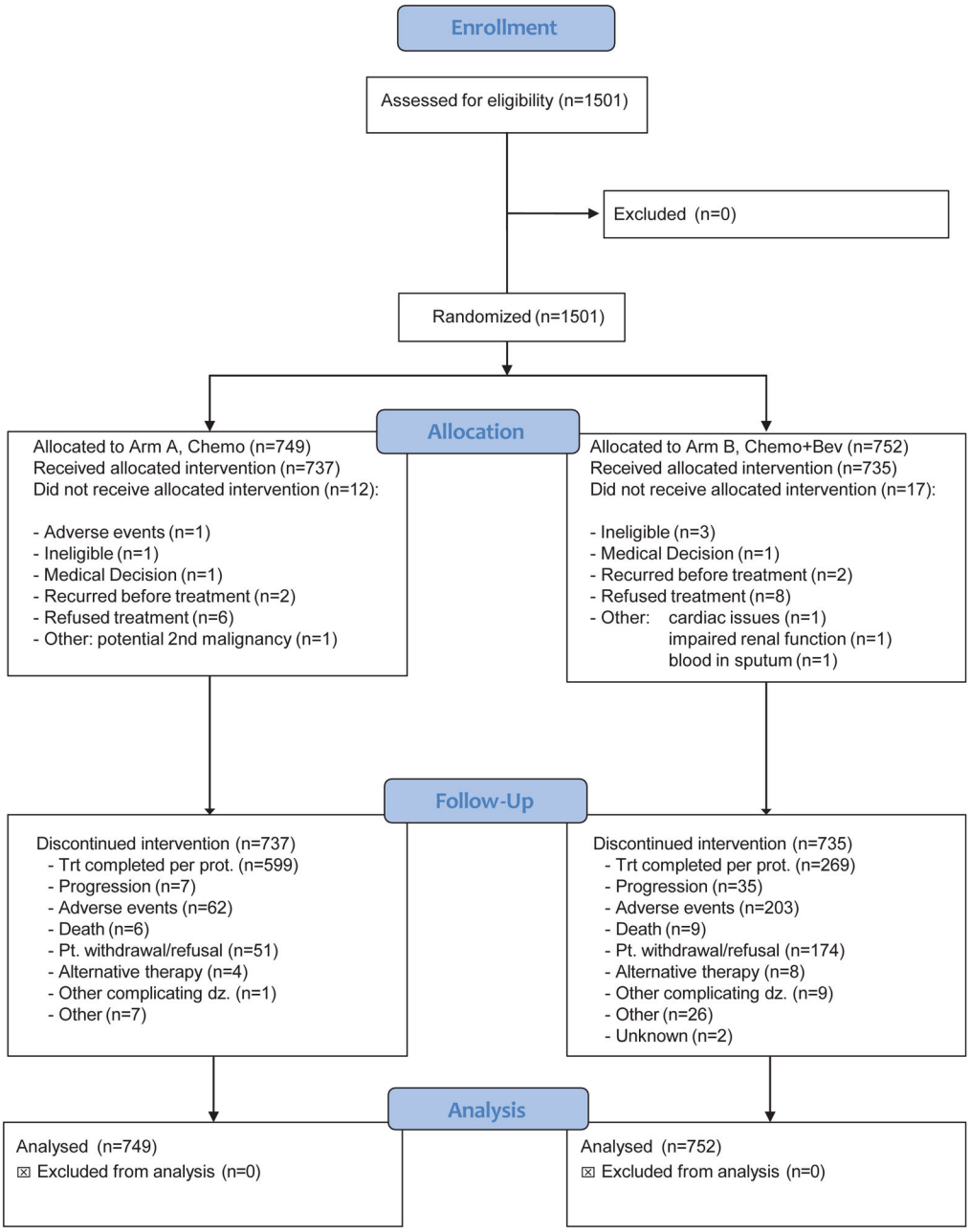
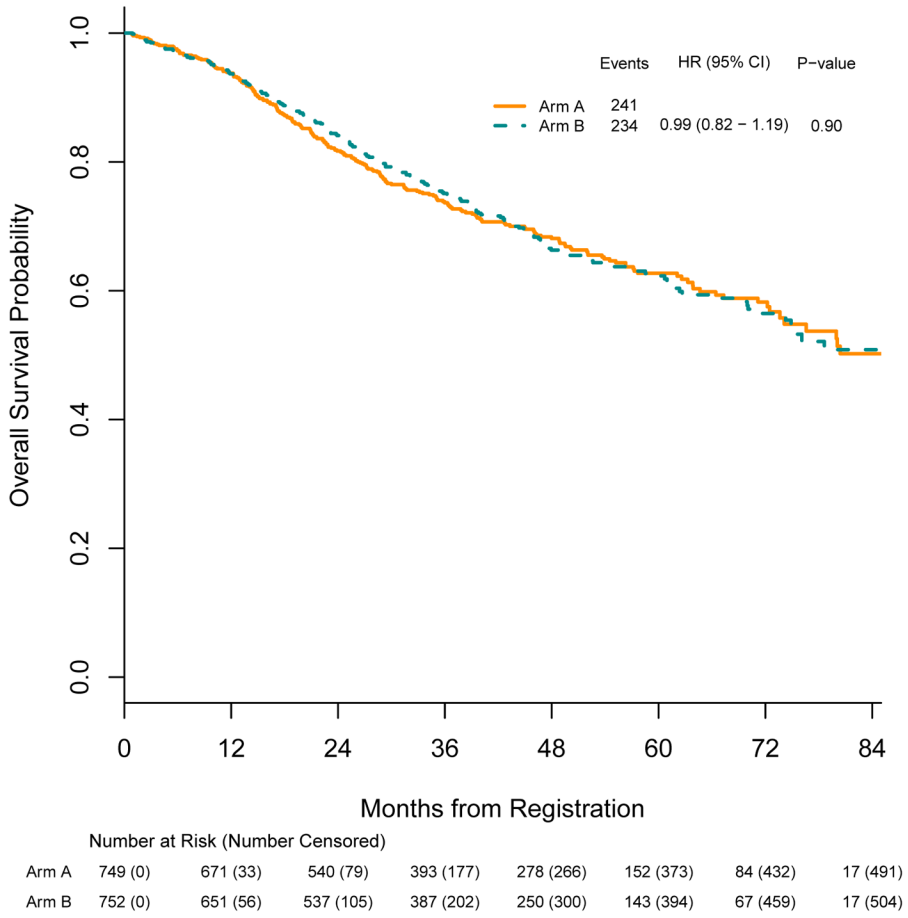


Figure 1.
Trial Profile



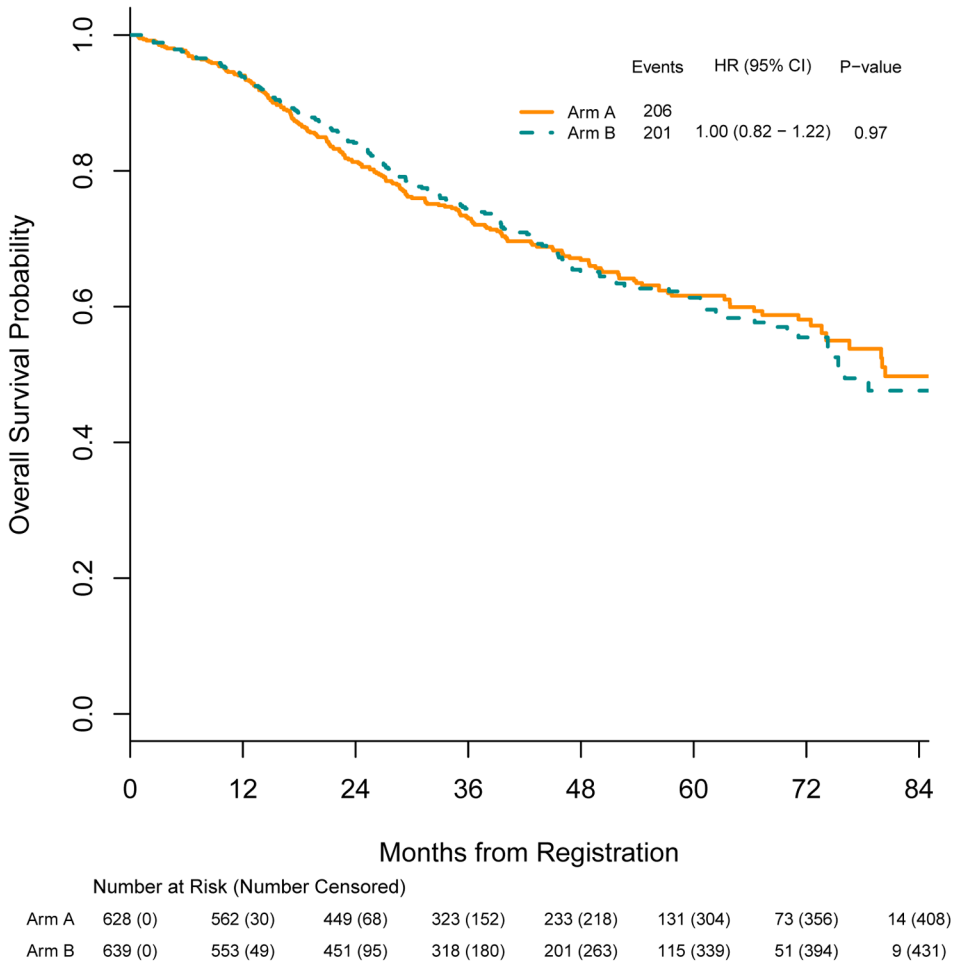


Figure 2.

Figure 2A: Overall survival by treatment arm for the primary analysis population (n=1501)

Figure 2B: Overall survival by treatment arm among eligible patients (n=1267)

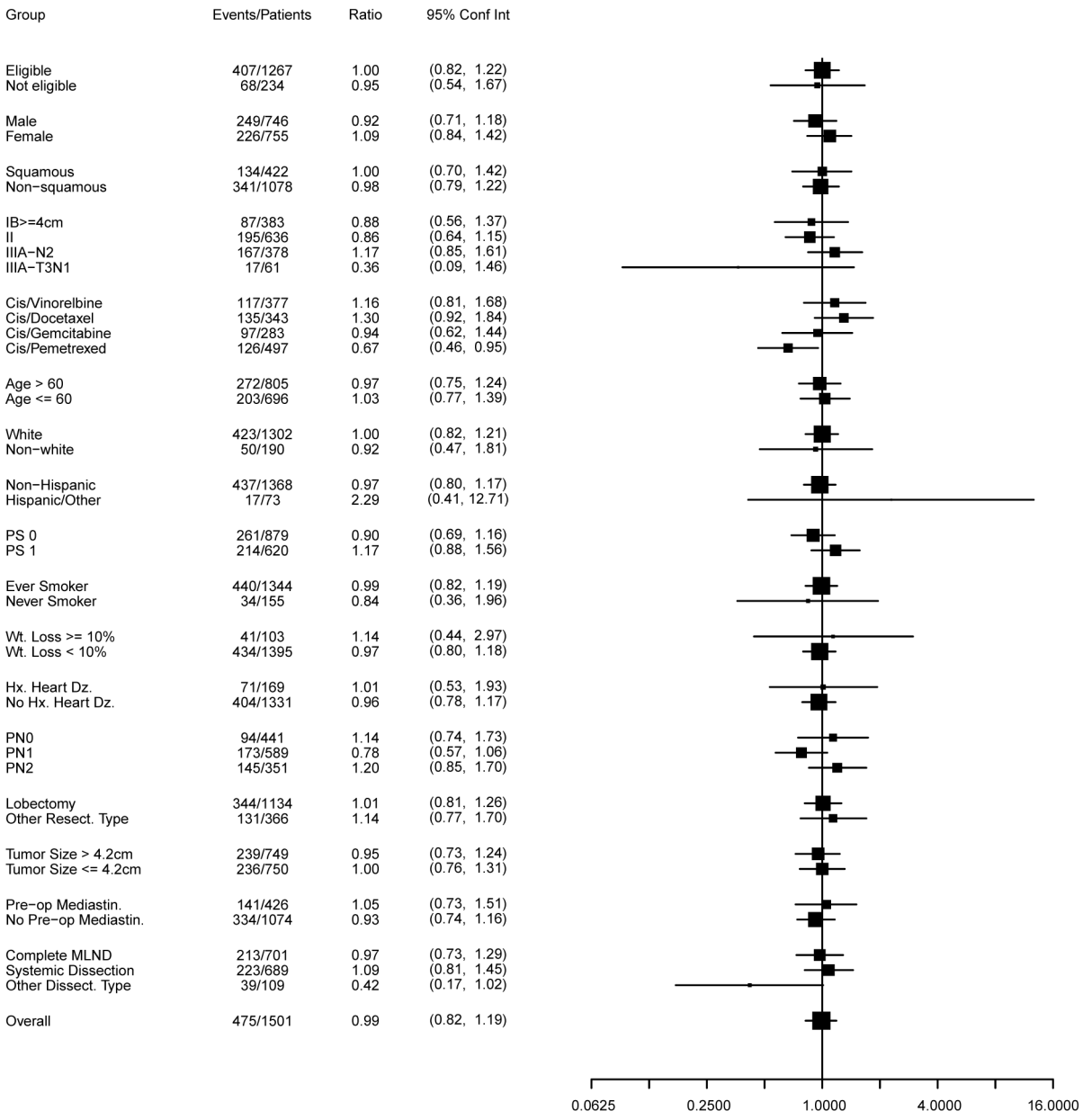
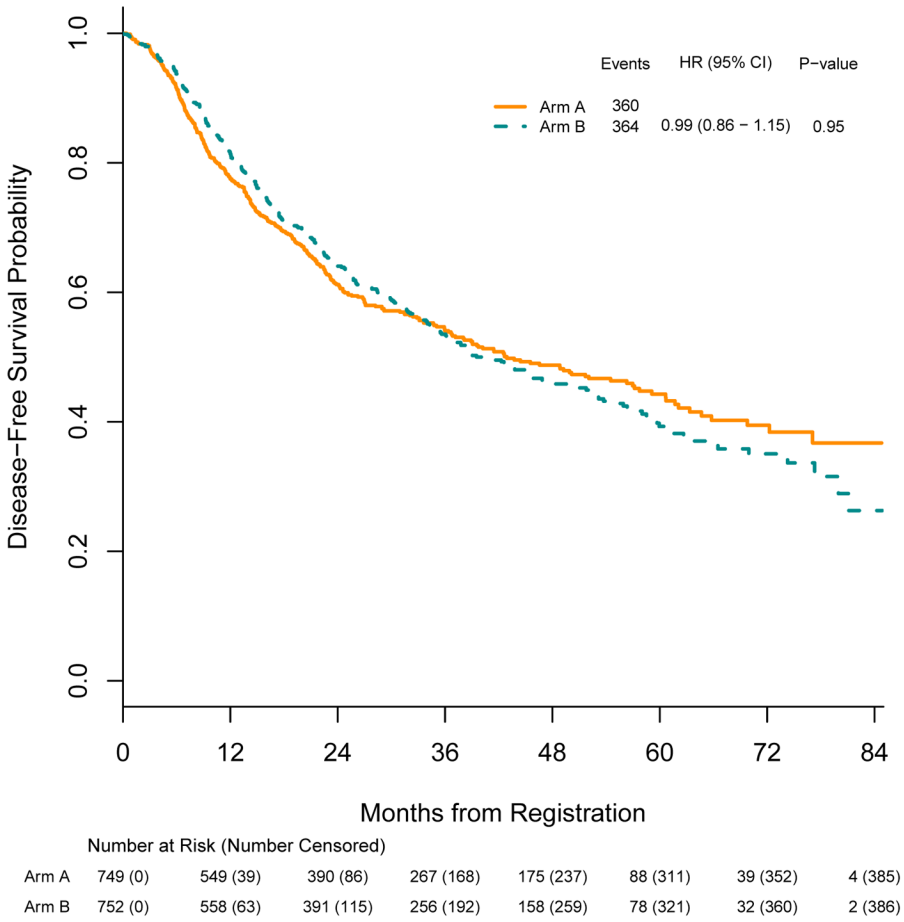


Figure 3.

A forest plot of overall survival hazard ratios for various subgroups



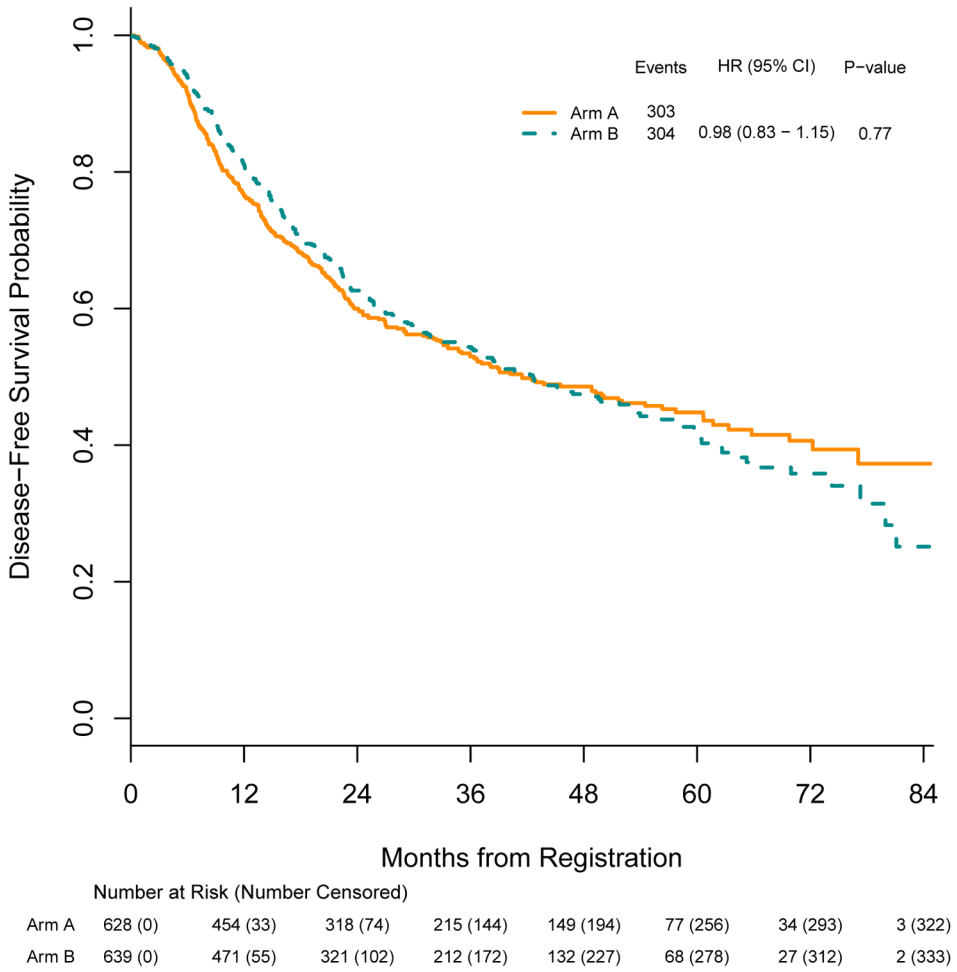


Figure 4.

Figure 4A: Disease-free survival by treatment arm for the primary analysis population (n=1501)

Figure 4B: Disease-free survival by treatment arm for the eligible patient population (n=1267)

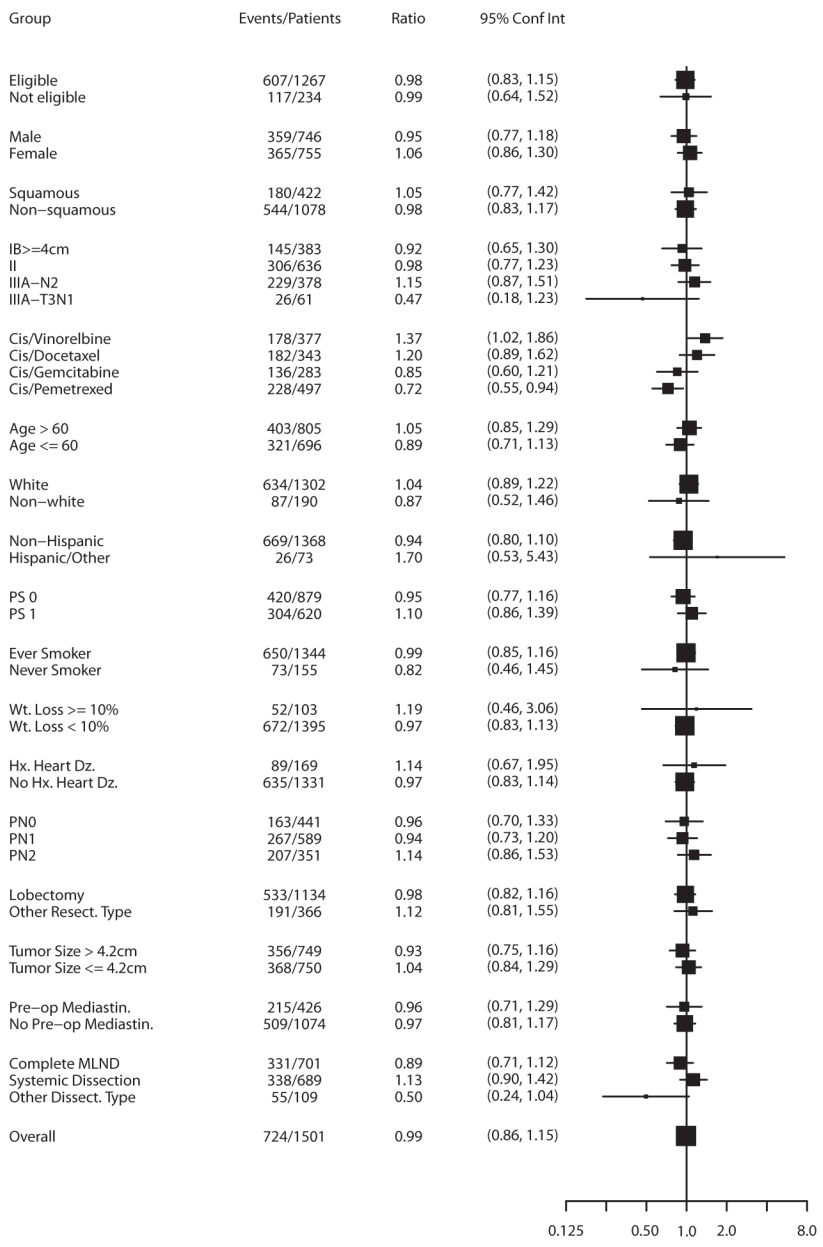


Figure 5.
A forest plot of DFS hazard ratios for various subgroups

Table 1

Demographics

Patient Characteristics			
		Arm A (Chemo) n=749	**Arm B (Chemo + Bev) n=752**
Age (Median)	Years	61 (IQR 55,67)	61(IQR 54,67)
Sex	Male	375/749 (50%)	371/752 (49%)
	Female	374/749 (50%)	381/752 (51%)
Race	White	642/746 (86%)	660/746 (88%)
	Black	74/746 (10%)	57/746 (8%)
	Asian	22/746 (3%)	16/746 (2%)
	Native Hawaiian	3/746 (<1%)	2/746 (<1%)
	Native American	1/746 (<1%)	5/746 (1%)
	Not reported	4/746 (1%)	6/746 (1%)
Chemo Regimen	Cisplatin/vinorelbine	187/749 (25%)	190/751 (25%)
	Cisplatin/Docetaxel	172/749 (23%)	171/751 (23%)
	Cisplatin/gemcitabine	142/749 (19%)	141/751 (19%)
	Cisplatin/pemetrexed	248/749 (33%)	249/751 (33%)
Histology	Squamous	216/749 (29%)	206/751 (27%)
	Adenocarcinoma	424/749 (57%)	450/751 (60%)
	Large Cell	22/749 (3%)	16/751 (2%)
	Other/Mixed	87/749 (12%)	79/751 (11%)
Stage (AJCC6)	IB T2N0	197/728 (27%)	186/730 (25%)
	IIA T1NI	83/728 (11%)	91/730 (12%)
	IIB T2N1	197/728 (27%)	197/730 (27%)
	IIB T3N0	27/728 (4%)	41/730 (6%)
	IIIA T3N1	29/728 (4%)	32/730 (4%)
	IIIA T1–3 N2	195/728 (27%)	183/730 (25%)
Surgery	Pneumonectomy	84/749 (11%)	108/751 (14%)
	Lobectomy	577/749 (77%)	557/751 (74%)
	Bilobectomy	59/749 (8%)	46/751 (6%)
	Complex lobectomy, Other	29/749 (4%)	40/751 (5%)

Table 2

Grade 1–2 events occurring in >=10% of patients

	Arm A	Arm B
Toxicity Type	**N(%)**	**N(%)**
Anemia	273 (37%)	202 (27%)
Fatigue	72 (10%)	77 (10%)
Creatinine increased	195 (26%)	276 (38%)
Neutrophil count decreased	243 (33%)	261 (36%)
WORST DEGREE	525 (71%)	567 (77%)
Anemia	273 (37%)	202 (27%)

Note: Grade 1 events were not reportable; grade 2 events were reportable only if deemed possibly related to bevacizumab treatment and unexpected.

Table 3

Post-Baseline Grade 3–5 Adverse Event Incidence ≥1%, All Attributions*

	A (n=738)			B (n=735)		
	Chemotherapy			Chemo + Bev		
	Grade			Grade		
	3	4	5	3	4	5
Adverse Event Type	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hearing impaired	8 (1%)	-	-	3 (<1%)	-	-
Tinnitus	4 (1%)	-	-	4 (1%)	-	-
Anemia	54 (7%)	-	-	48 (7%)	2 (<1%)	-
Febrile neutropenia	28 (4%)	3 (<1%)	-	37 (5%)	5 (1%)	1 (<1%)
Myocardial infarction	2 (<1%)	1 (<1%)	-	7 (1%)	1 (<1%)	2 (<1%)
Death NOS	-	-	4 (1%)	-	-	5 (1%)
Fatigue	73 (10%)	-	-	103 (14%)	2 (<1%)	-
Non-cardiac chest pain	17 (2%)	-	-	17 (2%)	-	-
Rash maculo-papular	1 (<1%)	-	-	4 (1%)	-	-
Abdominal pain	9 (1%)	-	-	30 (4%)	-	-
Colitis	5 (1%)	1 (<1%)	-	2 (<1%)	-	-
Constipation	13 (2%)	-	-	5 (1%)	-	-
Diarrhea	20 (3%)	1 (<1%)	-	40 (5%)	2 (<1%)	-
Mucositis oral	4 (1%)	-	-	12 (2%)	-	-
Nausea	62 (8%)	1 (<1%)	-	76 (10%)	-	-
Vomiting	38 (5%)	1 (<1%)	-	49 (7%)	1 (<1%)	-
Anaphylaxis	7 (1%)	-	-	6 (1%)	-	-
Bronchial infection	3 (<1%)	-	-	6 (1%)	-	-
Catheter related infection	1 (<1%)	-	-	5 (1%)	1 (<1%)	-
Enterocolitis infectious	3 (<1%)	-	-	7 (1%)	1 (<1%)	-
Lung infection	16 (2%)	-	-	24 (3%)	-	2 (<1%)
Sepsis	1 (<1%)	3 (<1%)	1 (<1%)	-	6 (1%)	1 (<1%)

	A (n=738)			B (n=735)		
	Chemotherapy			Chemo + Bev		
	Grade			Grade		
	3	4	5	3	4	5
Adverse Event Type	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Tooth infection	-	-	-	4 (1%)	-	-
Upper respiratory infection	2 (<1%)	-	-	5 (1%)	-	-
Urinary tract infection	5 (1%)	1 (<1%)	-	7 (1%)	-	-
Infections and infestations - Other	11 (1%)	1 (<1%)	-	13 (2%)	6 (1%)	-
Vascular access complication	10 (1%)	-	-	2 (<1%)	2 (<1%)	-
Creatinine increased	6 (1%)	1 (<1%)	-	10 (1%)	1 (<1%)	-
INR increased	4 (1%)	-	-	2 (<1%)	-	-
Lymphocyte count decreased	7 (1%)	-	-	12 (2%)	1 (<1%)	-
Neutrophil count decreased	117 (16%)	124 (17%)	-	128 (17%)	147 (20%)	-
Platelet count decreased	14 (2%)	16 (2%)	-	35 (5%)	12 (2%)	-
White blood cell decreased	29 (4%)	13 (2%)	-	23 (3%)	20 (3%)	-
Anorexia	11 (1%)	-	-	20 (3%)	1 (<1%)	-
Dehydration	45 (6%)	-	-	57 (8%)	1 (<1%)	-
Hyperglycemia	18 (2%)	6 (1%)	-	24 (3%)	2 (<1%)	-
Hyperkalemia	7 (1%)	-	-	5 (1%)	1 (<1%)	-
Hypoalbuminemia	1 (<1%)	-	-	4 (1%)	-	-
Hypocalcemia	4 (1%)	-	-	9 (1%)	2 (<1%)	-
Hypokalemia	25 (3%)	2 (<1%)	-	19 (3%)	4 (1%)	-
Hypomagnesemia	5 (1%)	-	-	5 (1%)	-	-
Hyponatremia	53 (7%)	3 (<1%)	-	77 (10%)	11 (1%)	-
Hypophosphatemia	1 (<1%)	-	-	4 (1%)	-	-
Arthralgia	7 (1%)	-	-	9 (1%)	-	-
Back pain	3 (<1%)	-	-	8 (1%)	-	-
Bone pain	1 (<1%)	-	-	8 (1%)	-	-
Generalized muscle weakness	8 (1%)	-	-	9 (1%)	-	-

	A (n=738)			B (n=735)		
	Chemotherapy			Chemo + Bev		
	Grade			Grade		
	3	4	5	3	4	5
Adverse Event Type	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Myalgia	6 (1%)	-	-	5 (1%)	-	-
Ataxia	2 (<1%)	-	-	5 (1%)	-	-
Dizziness	6 (1%)	-	-	14 (2%)	-	-
Headache	11 (1%)	-	-	28 (4%)	-	-
Peripheral sensory neuropathy	7 (1%)	-	-	8 (1%)	-	-
Seizure	4 (1%)	-	-	3 (<1%)	-	-
Syncope	15 (2%)	-	-	15 (2%)	-	-
Nervous system disorders - Other	1 (<1%)	2 (<1%)	-	2 (<1%)	5 (1%)	-
Confusion	4 (1%)	-	-	5 (1%)	-	-
Depression	4 (1%)	1 (<1%)	-	7 (1%)	2 (<1%)	-
Cough	5 (1%)	-	-	13 (2%)	-	-
Dyspnea	24 (3%)	2 (<1%)	-	45 (6%)	5 (1%)	-
Epistaxis	2 (<1%)	-	-	5 (1%)	-	-
Hypoxia	2 (<1%)	1 (<1%)	-	11 (1%)	2 (<1%)	1 (<1%)
Pneumonitis	4 (1%)	2 (<1%)	-	4 (1%)	1 (<1%)	-
Acute kidney injury	7 (1%)	-	-	5 (1%)	3 (<1%)	-
Chronic kidney disease	1 (<1%)	-	-	4 (1%)	-	-
Proteinuria	2 (<1%)	-	-	18 (2%)	-	-
Hypertension	60 (8%)	-	-	211 (29%)	8 (1%)	-
Hypotension	8 (1%)	1 (<1%)	-	11 (1%)	-	-
Thromboembolic event	12 (2%)	17 (2%)	2 (<1%)	16 (2%)	20 (3%)	-
WORST DEGREE	312 (42%)	169 (23%)	15 (2%)	378 (51%)	213 (29%)	19 (3%)

* Note that toxicity forms were submitted for one patient on Arm A even though this patient never started assigned therapy.